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Case-ascertained study of household transmission of seasonal influenza — South Africa, 2013

Preetha Iyengar[a,b,c,*], **Claire von Mollendorf**[d,e], **Stefano Tempia**[f,g], **Alexandra Moerdyk**[d], **Ziyaad Valley-Omar**[d], **Orienka Hellferscee**[d], **Neil Martinson**[h], **Meera Chhagan**[i], **Meredith McMorrow**[c,g], **Manoj Gambhir**[j,k], **Simon Cauchemez**[l], **Ebrahim Variava**[m], **Katlego Masonoke**[h], **Adam L. Cohen**[c,f,g], and **Cheryl Cohen**[d,e,**]

[a]Epidemic Intelligence Service, Centers for Disease Control and Prevention, 1600 Clifton Rd, Atlanta, GA, USA

[b]Global Disease Detection Branch, Division of Global Health Protection, Centers for Disease Control and Prevention, 1600 Clifton Rd, Atlanta, GA, USA

[c]US Public Health Service, 5600 Fishers Ln, Rockville, MD, USA

[d]Centre for Respiratory Diseases and Meningitis, National Institute for Communicable Diseases, 1 Modderfontein Rd, Sandringham, Johannesburg, South Africa

[e]School of Public Health, Faculty of Health Science, University of the Witwatersrand, 1 Jan Smuts Avenue, Braamfontein, Johannesburg, South Africa

[f]Influenza Program, Centers for Disease Control and Prevention—South Africa, PO Box 9536, Pretoria, South Africa

[g]Influenza Division, Centers for Disease Control and Prevention, 1600 Clifton Rd, Atlanta, GA, USA

[h]Perinatal HIV Research Unit, University of the Witwatersrand, Johns Hopkins University Center for TB Research, 1550 Orleans Street, Baltimore, MD, USA

[i]Department of Pediatrics, University of KwaZulu-Natal, King George V Ave, Glenwood, Durban, South Africa

[j]Modeling Unit, National Center for Immunization and Respiratory Disease, Centers for Disease Control and Prevention, 1600 Clifton Rd, Atlanta, GA, USA

[k]Epidemiological Modelling Unit, Department of Epidemiology and Preventive Medicine, Monash University, 99 Commercial Road, Melbourne, Australia

[*]Corresponding author. Save the Children, 2000 L St NW Suite 500, Washington DC 20036, USA. Tel.: +1 202 640 6863. piyengar@gmail.com (P. Iyengar). [**]Corresponding author. Centre for Respiratory Diseases and Meningitis (CRDM), National Institute for Communicable Diseases, 1 Modderfontein Rd Sandringham, Johannesburg 2193, South Africa. Tel.: +27 11 386 6593. cherylc@nicd.ac.za (C. Cohen).

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The findings and conclusions of this report are that of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Conflict of interest

The authors declare no commercial or other associations that might pose a conflict of interest.

[l]Mathematical Modelling of Infectious Diseases Unit, Institut Pasteur, 28 rue du Docteur Roux, Paris, France

[m]Department of Medicine, Klerksdorp Tshepong Hospital Complex and University of the Witwatersrand, Corner of OR Tambo and John Orr Street, Klerksdorp, South Africa

Summary

Objectives—The household is important in influenza transmission due to intensity of contact. Previous studies reported secondary attack rates (SAR) of 4–10% for laboratory-confirmed influenza in the household. Few have been conducted in middle-income countries.

Methods—We performed a case-ascertained household transmission study during May–October 2013. Index cases were patients with influenza-like-illness (cough and self-reported or measured fever (≥38 °C)) with onset in the last 3 days and no sick household contacts, at clinics in South Africa. Household contacts of index cases with laboratory-confirmed influenza were followed for 12 days.

Results—Thirty index cases in 30 households and 107/110 (97%) eligible household contacts were enrolled. Assuming those not enrolled were influenza negative, 21/110 household contacts had laboratory-confirmed influenza (SAR 19%); the mean serial interval was 2.1 days (SD = 0.35, range 2–3 days). Most (62/82; 76%) household contacts who completed the risk factor questionnaire never avoided contact and 43/82 (52%) continued to share a bed with the index case after illness onset.

Conclusion—SAR for laboratory-confirmed influenza in South Africa was higher than previously reported SARs. Household contacts did not report changing behaviors to prevent transmission. These results can be used to understand and predict influenza transmission in similar middle-income settings.

Keywords

Influenza; Secondary infection risk; Household transmission; Serial interval; South Africa

Background

The household plays an important role in influenza transmission due to the high frequency and intensity of contact. It has been estimated that in the US, approximately 30% of transmission occurs in the household.[1] The household also provides a useful setting to track influenza infections among close contacts of cases because the number of individuals exposed to the index case can be defined, exposure is likely similar, and identification of household contacts is logistically feasible.

Prior transmission studies with secondary cases of laboratory-confirmed seasonal and pandemic influenza have shown secondary infection risk (SIR) among household contacts to range from 4 to 10% when based on laboratory-confirmed illness,[2–4] and from 13 to 30% when estimated based on symptoms.[1,3,5–8] Thus far, the mean estimated serial interval found in household transmission studies on influenza has been 2–4 days.[2,9–13] To date there have been few reports on household transmission of seasonal influenza in middle-income

countries such as South Africa.[14–18] South Africa has a temperate climate and influenza is highly seasonal circulating in the Southern hemisphere winter between May and September each year.[19] The estimated annual incidence of influenza-associated hospitalization for lower respiratory tract infection was approximately 50 per 100,000 population during non-pandemic years (2010–2011), and data from national surveillance indicate that 9% of patients hospitalized for acute lower respiratory tract infections had respiratory specimens that tested positive for influenza.[20] However, there are few data describing the household transmission of influenza virus in South Africa.[14]

We aimed to determine the SIR, serial interval, and associated risk factors for influenza transmission in household contacts of individuals infected with seasonal influenza in communities in South Africa.

Methods

We performed a case-ascertained household transmission study during May–October 2013.

Population

The study was conducted in two locations in South Africa: Klerksdorp and Pietermaritzburg. Klerksdorp, located in the local municipality of Matlosana in North West Province, has a population of over 335,000 people and is 115 km^2 in area.[21] The city of Klerksdorp is surrounded by 5 townships, which are organized into extensions that include mostly single-family houses and shacks (informal dwellings). Pietermaritzburg, located in the municipality of Msunduzi in KwaZulu-Natal Province, has a population of 618,536, and spans 659 km^2 in area.[22] Both are peri-urban settings. The study population included all individuals who sought care at selected local public health facilities and were infected with influenza virus (the index case), and their household contacts.

Recruitment

Index cases and their household contacts were recruited from 6 community clinics: four clinics in Klerksdorp, North West Province (Jouberton, Tshepong Gateway, Alabama, and Park Street clinic), and two in Pietermaritzburg, KwaZulu-Natal Province (Embalenhle and Edendale Gateway clinics). Patients who presented at the selected clinics with: (i) influenza-like-illness (ILI; defined as measured fever of ≥38 °C or self-reported fever and cough, with onset within the last three days); (ii) who had a positive rapid influenza diagnostic test (RIDT) at the point of care using the Becton Dickinson (BD) Veritor™ system Flu A+B RIDTs; (iii) no currently ill household contacts; and (iv) lived with at least 2 household contacts, were considered eligible index cases, and were enrolled in the study. RIDTs were later confirmed by real-time reverse transcription polymerase chain reaction (rRT-PCR). Enrolled index cases with initially positive RIDT but negative rRT-PCR and their household contacts were removed from the study. Human immunodeficiency virus (HIV) status for index cases was determined by rapid HIV testing or review of medical records; a negative HIV test result from the last 6 weeks was considered valid.

A household was a group of two or more people who regularly ate or slept in the same residence four or more days a week (residential institutions were excluded); an eligible

household contact was defined as any person who regularly eats or sleeps in the same household as the index case four or more days a week during the exposure period (one day before to twelve days after onset of illness in the index case). A currently ill household contact was defined as a household contact reporting fever and cough within the last 7 days.

Follow-up

Enrolled household contacts were recruited within 48 h of index patient recruitment and followed for 12 days. Follow-up visits occurred in the home or the clinic on days 4, 8, and 12 after the index case was enrolled. Nasopharyngeal (NP) swabs were collected from all household contacts and index cases at each visit. Trained personnel administered baseline questionnaires. Interviews for index cases occurred at the time of enrollment, and for household contacts at the initial visit to collect information on demographics, medical conditions, ILI symptoms, medication usage, and frequency of contact between household contacts and the index case.

At each visit, a brief follow-up questionnaire assessing frequency of contact with the index case, presence of symptoms, and health care utilization was administered. Diaries were provided to each household contact to record frequency of contact with the index case and presence or absence of ILI symptoms daily. If the follow-up visit fell on a Sunday, the visit occurred on Saturday or Monday. If a household contact was unavailable, the study teams attempted two re-visits. If two visits were missed, the household contact was removed from the study. Participants were compensated for transport to the clinic for follow-up visits.

Laboratory methods

NP swab samples collected during home visits were stored in cooler boxes with ice packs, and then taken to the nearest recruitment clinic for storage in a 4 °C refrigerator. Samples were transported to the National Institute for Communicable Diseases (NICD) in Johannesburg within the next 48 h, where total nucleic acid extraction was performed on the MagNA Pure 96 instrument. All specimens were tested for influenza virus A and B (InfA and InfB) as described by Pretorius et al.[23] Household contact samples confirmed positive for InfA and InfB were then transported to the laboratory in Groote Schuur Hospital, University of Cape Town, for further analysis. Influenza A-positive samples were subtyped for seasonal (A(H1N1), A(H3N2)) and pandemic (A(H1N1)pdm09) influenza viruses by rRT-PCR using the CDC Influenza Virus protocol.[24]

Outcome measures

Outcomes in household contacts were categorized as having no respiratory illness, ARI or laboratory-confirmed influenza. We defined *laboratory-confirmed* contacts as persons with a positive result for influenza by rRT-PCR testing of one or more NP specimens collected during follow-up that corresponded to the influenza type of the index case, regardless of symptoms. We defined *ARI* using a definition similar to prior transmission studies,[2] as reporting of any of two symptoms (fever, sore throat, cough/difficulty breathing, aches/pains in muscles or joints, nasal congestion/runny nose/sneezing, diarrhea, or headache) on a given day.

Statistical analysis

The household SIR was estimated as the proportion of eligible household contacts that had laboratory-confirmed influenza (same subtype) and for contacts with ARI regardless of laboratory-confirmation. All eligible contacts were used to calculate SIR to ensure that all persons of known exposure to the index case were included in the analysis. Eligible contacts that refused enrollment were assumed to be negative so as to not falsely elevate the SIR. A sensitivity analysis was performed in which non-enrolled eligible contacts were excluded to explore the effect of this assumption. The serial interval was defined as the duration of time between onset of symptoms in the index case and onset of symptoms in a symptomatic household contact.[10] Proportions were compared using the chi-squared or Fisher's Exact test. Analyses were performed in SAS 9.3 (SAS Institute, Cary, NC).

Ethics statement

Ethical approval was obtained from the University of the Witwatersrand and KwaZulu-Natal, and from the Centers for Disease Control and Prevention with reliance on these ethical approvals. Written informed consent or assent was obtained from all participants or their caregivers.

Results

Thirty index cases were enrolled and 110 eligible household contacts were identified (Fig. 1). Seven (23%) index cases were ≥5 years of age and had 20 household contacts; 23 (77%) index cases were >5 years of age and had 90 household contacts. We had complete laboratory data for all 30 index cases, and completed questionnaires for 29 index cases. Of the 110 eligible household contacts, 107 (97%) were enrolled. Three household contacts declined due to lack of availability for follow-up visits, however consented to completing symptom and contact diaries. Baseline questionnaires were completed for 106 (99%) of 107 enrolled household contacts and risk factor questionnaires were completed by 87 (81%) of 107 enrolled household contacts.

Households had a median of 5 (range 3–7) members including the index case, 5 total rooms (range 1–9), and 3 (range 1–7) rooms for sleeping (Table 1). Sixty-six percent (19/29) of index cases were female with a median age of 16 years (IQR 6–37) and 30% (9/29) were confirmed to be HIV-infected by laboratory testing (Table 2). Sixty percent (64/106) of household contacts were female with a median age of 23 years (IQR 12–43); 11% (12/106) were HIV-infected (3 tested, 8 from patient-held medical records, 1 self-report, 50 declined response) (Table 2). Among index cases, 3% (1/29) reported receiving one dose of influenza vaccine in the previous 12 months (which included the current influenza season). Amongst household contacts, 5% (5/106) reported having received one dose of the influenza vaccine in the previous year (including the current influenza season). At the beginning of the study, 27 (25%) household contacts reported sharing a bed with the index case, and 30 (28%) reported sharing a cup or plate with them. Of those who completed the risk factor questionnaires at the end of the study, most (62/82; 76%) reported that they had never avoided contact with the index patient and 43 (52%) had shared a bed with the index case during the study period.

Symptom diaries were completed by 82/110 (75%) eligible household contacts, and contact diaries by 74/110 (67%) eligible household contacts. Among responders, 60 reported new onset ARI during the study, yielding a SIR for ARI of 55% (CI 45–64%) (60/110) for all ages, assuming non-responders did not have symptoms. The median age of symptomatic household contacts was 19 years (IQR 11–39) and 38 (63%) were female. There was no significant difference in SIR for ARI in household contacts by age group of the index case (index cases ≥5 years SIR 43% (9/21) vs index cases >5 years SIR 55% (51/92) p = 0.34).

Of the 60 (55%) household contacts reporting ARI, 16 (27%) completed additional risk factor questions assessing change in behavior after symptom onset. Fourteen (88%) reported that they never avoided household contacts and 11 (73%) never slept in a separate bed from other household contacts after symptom onset. In addition, 14 (88%) never avoided school, work, or social gatherings to protect others from catching their illness. Twelve (75%) reported always or often covering their mouths when they coughed/sneezed.

Of the 107 enrolled household contacts, 24 (22%) were positive for influenza by rRT-PCR during the study period. In three cases, the subtype of the household contact did not match that of the index case, and those were excluded from the estimation of SIR as it was likely that this infection was due to transmission from the community and not the index case. There were no co-primary cases (household contacts reporting symptom onset on the same day as the index case). Eligible contacts who were not enrolled were assumed to be negative for influenza rather than excluded to ensure SIR would not be falsely elevated. There were 31 (29%) participants missing one laboratory sample, 7 (7%) missing two laboratory samples, and 1 (1%) missing three laboratory samples. In total, 21 of 110 household contacts (including asymptomatic cases) were positive for the same influenza subtype as the index case by rRT-PCR in 16 households and were included in the analysis, yielding a SIR for laboratory-confirmed influenza of 19% (CI 12–27%). Sensitivity analysis excluding the three eligible household contacts that were not enrolled from the analysis resulted in an SIR of 20% (CI 12–27%). Five households had two secondary cases, and 11 households had one secondary case. The median age of household contacts with laboratory-confirmed influenza was 18 years (IQR 3–51), and 11 (52%) were female. When stratified by age, the SIR for laboratory-confirmed influenza in household contacts with index cases ≥5 years old was 30%, and with index cases >5 years old was 17% (p = 0.17).

Of the 21 household contacts with laboratory-confirmed influenza, 18 were infected with influenza A. Of these, 9 (50%) were H1N1 subtype, 7 (39%) were H3N2 subtype, 2 were unable to be subtyped. The remaining 3 (14%) were influenza B. There was no significant difference in SIR by subtype (17% (H1N1), 16% (H3N2), and 21% (influenza B), p = 0.89).

Of the 21 laboratory-confirmed index cases, data on index case and household contact symptom onset were available for 8 index case-household contact pairs. The mean serial interval for transmission of laboratory-confirmed influenza was 2.1 days (standard deviation = 0.35, range 2–3 days; Fig. 2). Of the 60 cases with ARI, data on index and household contact symptom onset were available for 44 index case-household contact pairs. The mean serial interval for ARI was 2 days (standard deviation = 2.3, range 1–11 days; Fig. 2).

Fifteen (71%) of the 21 household contacts with laboratory-confirmed influenza completed symptom diaries. Of these 15, 3 (20%) were asymptomatic. The most common symptoms reported by household contacts with laboratory-confirmed influenza were cough (14/15, 93%), nasal discharge (13/15, 87%), and fever (10/15, 67%). Overall, of the 60 who reported symptoms (including laboratory-confirmed influenza and ARI), the most common symptoms were cough (51/60, 85%), nasal discharge (48/60, 80%), and myalgia (38/60, 63%). Other symptoms reported included headache, sore throat, and diarrhea. Diarrhea was the least commonly reported symptom amongst both those with laboratory-confirmed influenza (3/21, 14%) and those with ARI (18/60, 30%).

Of the 21 household contacts with laboratory-confirmed influenza, 13 (62%) completed contact diaries. Table 3 shows the amount of time spent and activities done with the index case for laboratory-confirmed influenza cases and household contacts without influenza during the first 3 days of enrollment. On Day 3 of the study, more household contacts with confirmed influenza reported spending most of the day in the home with the index case than well household contacts ($p = 0.01$). There were no other significant differences between household contacts with or without laboratory-confirmed influenza on time spent or activities done with the index case (Table 3).

Discussion

We found an SIR of 19% for laboratory-confirmed seasonal influenza in South African households. This is higher than in prior studies in other countries, which range from 4 to 10%.[2–4] This difference in infection risk could be due to many factors that have been shown to be risk factors for increased influenza transmission, such as younger age of index case, larger number of household members, and crowded sleeping conditions, which may occur more frequently in low and middle-income settings.[9,15,25]

Our SIR for ARI (55%) was much higher than what we found for laboratory-confirmed influenza (19%), but similar to what was seen when comparing studies that report SIR based on ARI alone[1,3,5–8] versus those which are laboratory-confirmed. [2,3] However in ARI, unlike with laboratory-confirmed cases, we were unable to exclude cases that may not have been related to the index cases. SIR for ARI of up to 38% and for laboratory-confirmed influenza up to 13% have been reported in prior studies.[1,3,6–8] Our findings are consistent with the range of results reported by a study done on pandemic influenza in South Africa.[14] In that study, the authors were unable to perform confirmatory testing on all cases, but estimated a SIR of pandemic influenza ranging from 10% (laboratory-confirmed cases) to 17% (including symptomatic cases who did not have confirmatory testing), and a serial interval of transmission of 2.3 days.[14]

In contrast a previous study in Hong Kong[10] showed that 80% (12/15) of laboratory-confirmed contacts who completed symptom diaries reported symptoms. This may indicate that asymptomatic carriers may not be a driver of transmission in these communities. This indicates that laboratory-confirmation, while difficult, is important in giving a more accurate picture when calculating SIR. As there are typically many respiratory viruses circulating during the winter season,[23] it is not surprising that there is a high rate of ARI in individuals

testing influenza negative. Similar to other studies[2,4,9,26], our study reported a higher SIR in laboratory-confirmed cases when the index case was ≥5 years old, although this was not statistically significant, likely due to low numbers of enrolled cases.

A study in Mongolia, which similar to South Africa is a low to middle-income country, found a much lower SIR of 6%; however, Mongolia is a sparsely populated country that may have less household crowding.[26] In our study 15 (50%) households reported having 2 or more people share a room for sleeping, which has been found to be a risk factor for secondary influenza transmission.[25] A study done in a similar setting in Kenya found a SIR of 8%,[18] similar to prior studies but less than what was found in our study; however, this study was unable to account for asymptomatic cases or provide laboratory-confirmation. The Kenya study also indicated that household contacts of HIV-infected index cases may be at higher risk of developing secondary ILI, which may be relevant in the communities in which our study was conducted due to the high HIV prevalence.[27] Our study also showed time spent in the home with the index case on Day 3 of the study was a risk factor for influenza infection. This indicates that increased exposure to the index case through contact is a risk factor, however our sample size was too small to demonstrate this consistently.

Our study has limitations that warrant discussion. The case-ascertainment study design has inherent bias as only patients coming to the clinic to seek care within the first 3 days of illness could be included.[2] These patients could have more severe or infectious illness that may have falsely elevated the SIR in this population.[2] Screening cases for inclusion with RIDT may have led us to fail to identify some potentially eligible index cases because of low sensitivity of these tests.[28] Also, although HIV infection status of household contacts has been suggested as a risk factor for influenza transmission, we were not able to examine this due to small sample size and missing data on HIV infection status for approximately half of the household contacts. Our analysis also assumed similar exposure for all household contacts, which may not have been the case. While data was collected on interactions and activities of household contacts with the index cases, small sample size and missing data did not allow us to perform an adjusted analysis to look for differences in exposure and risks. The assumption was also made that secondary cases with the same type of influenza as the index case were due to household transmission and not from the community, however this is supported by prior studies showing that risk of infection is much higher in the household.[29] As study teams only interacted with the families every 3 days, if a form was not filled out daily, there may have been recall bias when reporting symptoms and interactions with the index case. Strengths of our study include that our study is based on laboratory-confirmed findings in addition to symptom report, close follow-up of contacts, and testing of asymptomatic individuals.

Conclusions

This is the first household transmission study on seasonal influenza in South Africa. SIR for laboratory-confirmed influenza and ARI were higher than what has been reported in previous studies and studies from other countries,[2–4] but are consistent with the study done in South Africa on pandemic influenza.[14] There is a large burden of respiratory symptoms in this community, yet household contacts did not report changing behaviors to prevent

transmission, influenza vaccination rates were low, and risk factors of crowded sleeping conditions and spending time in the home with the index case were reported. Education on transmission-reducing behaviors could guide public health measures to improve influenza transmission control in households in similar settings. This study provides local data on influenza transmission that can be used to understand and predict influenza transmission through modeling in similar middle-income community settings.

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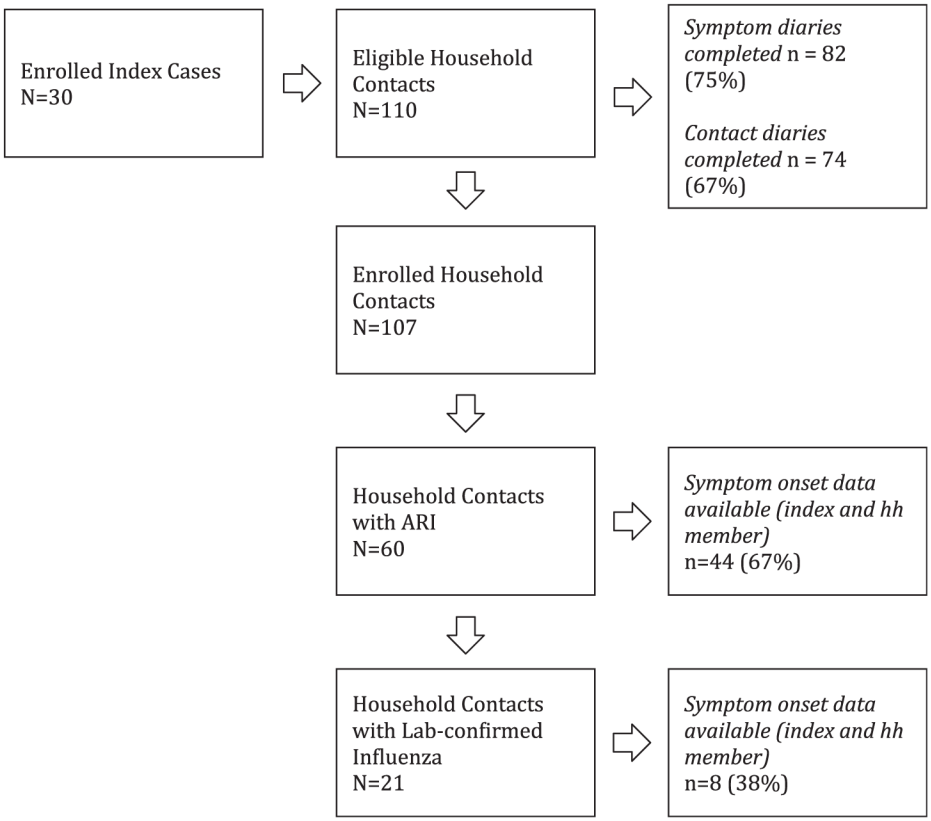

Figure 1.
Enrollment and outcomes of index cases and household contacts — South Africa, 2013.

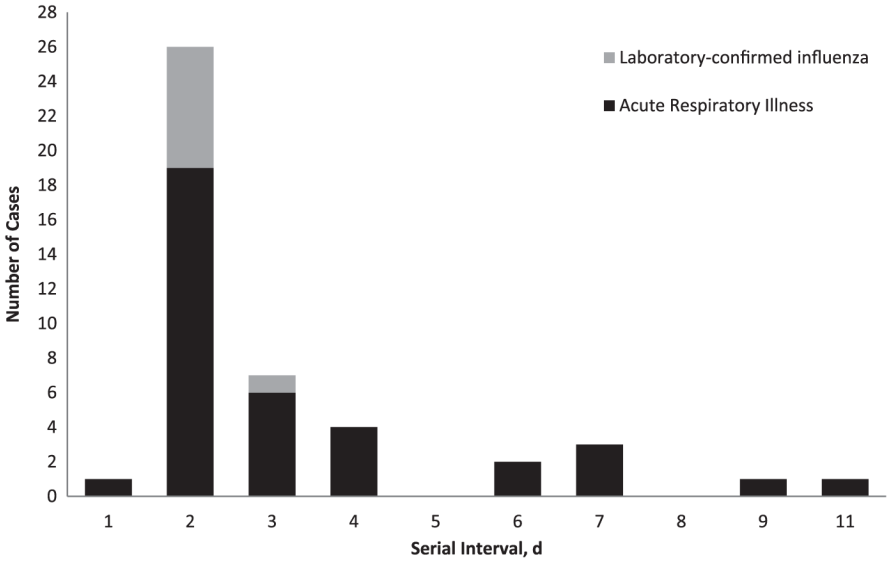

Figure 2.
Serial interval of transmission for laboratory-confirmed influenza and acute respiratory illness — South Africa, 2013.

Table 1

Characteristics of enrolled households — South Africa, 2013.

Characteristic	**N = 30 Median (range)**
Number of household members	5 (3–7)
Total number of rooms in house	5 (1–9)
Total number of rooms for sleeping in house	3 (1–7)
Characteristic	n (%)
Smoke exposure in the home daily	8 (27)
Home has area to wash hands	23 (85)
Main area to wash hands is tap outside	11 (37)
Main water source is outdoor tap	20 (67)
Soap available for hand washing	20 (67)
Cook with electric stove	29 (97)

Table 2

Baseline demographics and past medical history for enrolled index cases and household contacts — South Africa, 2013.[a]

Demographics	Index cases, N = 29 n (%) or median (IQR)	Household contacts, N = 106 n (%) or median (IQR)	p-Value
Sex (Female)	19 (63)	64 (60)	0.70
Age	16 years (6–37)	23 years (12–43)	0.11
Relationship to index case	–	44 (42) other relative	–
		20 (19) parent	
		18 (17) spouse	
Share a bed with index case	–	27 (25)	–
Share cup or plate with index case	–	30 (28)	–
Occupation			
Student	11 (38)	41 (39)	0.52
In primary or secondary school	8 (28)	29 (27)	0.52
Highest level of education attained (if not in school)[b]	3 (10) primary school	31 (29) secondary school	1
	3 (10) secondary school	13 (12) primary school	0.12
	3 (10) matriculation/university	9 (9) matriculation/university	0.46
Not working	6 (21)	42 (40)	0.17
Past medical history[c]			
Alcohol use	5 (17)	15 (14)	0.87
Cigarette use	1 (3)	17 (16)	0.32
HIV positive	9 (31)	12 (11)[d]	0.31
Currently taking antiretrovirals (% of HIV positive)	3 (10)	8 (8)	0.20
Currently on treatment for TB	1 (3)	2 (2)	1
Currently taking antibiotics	1 (3)	13 (12)	0.30
Received 1 dose of influenza vaccine	1 (3)	5 (5)	1
Stroke	0	1 (1)	1
Heart failure	0	1 (1)	1
Pregnancy	0	2 (2)	1
Diabetes	0	3 (3)	0.96
Seizure disorder	0	1 (1)	1

[a] IQR = interquartile range; TB = tuberculosis; HIV = human immunodeficiency virus.

[b] Only top three responses shown.

[c] Only medical conditions with positive responses listed.

[d] 50 household contacts declined to provide HIV status.

Table 3

Time spent and activities done with enrolled index case in study days 0*–3 — South Africa, 2013.

		Day 0	Day 1	Day 2	Day 3
Spent most of the day in the same home	Confirmed[a]	10 (77%)	8 (62%)	7 (54%)	12 (92%)
	Well[b]	36 (59%)	35 (57%)	28 (46%)	36 (59%)
	p-value	0.20	0.30	0.52	0.01
Spent >5 h with index case	Confirmed[a]	10 (77%)	9 (69%)	9 (69%)	9 (69%)
	Well[b]	39 (64%)	41 (67%)	32 (52%)	31 (51%)
	p-value	0.74	0.72	0.51	0.51
Napped with index case	Confirmed[a]	6 (46%)	5 (38%)	6 (46%)	5 (38%)
	Well[b]	17 (28%)	15 (25%)	18 (30%)	17 (28%)
	p-value	0.20	0.32	0.33	0.51
Ate with index case	Confirmed[a]	9 (69%)	8 (62%)	8 (62%)	9 (69%)
	Well[b]	33 (54%)	33 (54%)	31 (51%)	32 (52%)
	p-value	0.37	0.76	0.55	0.36
Assisted with basic care	Confirmed[a]	1 (8%)	1 (8%)	1 (8%)	1 (8%)
	Well[b]	7 (11%)	8 (13%)	9 (15%)	7 (11%)
	p-value	1	1	0.68	1

*Day 0 is defined as the day the index case was enrolled in the study.

[a]Household contacts with laboratory-confirmed influenza, N = 13 (n, %).

[b]Well household contacts, N = 61 (n,%).